Naval Health Research Center Detachment (Toxicology)

A NEW PERSPECTIVE FOR IDENTIFYING POTENTIAL CARDIAC SENSITIZERS

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PREFACE

This is an interim report describing part of the research efforts at the Naval Health Research Center Detachment Toxicology (NHRC/TD) to construct either a single or series of mathematical model(s) that can predict a chemical's potential as a cardiac sensitizer. The model is based upon physiological measurements prior to the onset of cardiac arrhythmia. The measurements were separated into baseline and arrhythmicgenic responses. Ouabain, a digitalis glycoside, was selected for this study because of its ease of use and documentation as a cardiac sensitizer. This work was sponsored by the Naval Medical Research Command under Work Unit #63706N-M00095.004.1711 and was preformed under the direction of CAPT Kenneth R. Still, MSC, USN, Officer-in-Charge NHRC/TD.

The opinions contained herein are those of the author and are not to be construed as official or reflecting the view of the Department of the Navy or the Naval Services at large. The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals," as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Research, National Research Council, DHHS, National Institutes of Health. Publication 85-23, 1985 and the Animal Welfare Act of 1966, as amended.

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EXECUTIVE SUMMARY

PROBLEM

Cardiac sensitization is the sensitization of the heart to circulating catecholamines (i.e. epinephrine) after exposure to an exogenous chemical, such that sudden alarm or exercise may precipitate a cardiac arrest. The main mechanism of cardiac arrest is a cardiac arrhythmia, although anoxia, respiratory depression, and vagal stimulation along with aspiration of vomit or trauma may be contributing factors leading to sudden death. The most prevalent example of cardiac sensitization is the recreational abuse of solvents, commonly known as "Huffing" or "Sniffing". Chemicals that have a known cardiac sensitizing potential include: fuel gases (butane, propane, and gasoline vapors); other solvents such as typewriter correction and dry cleaning fluids (trichloroethane); fire extinguishers (bromochlorodifluoromethane); degreasing agents (trifluorotrichloroethane); adhesives (toluene); aerosol propellants (halons and/or butane); and medications (digitalis glycosides and cocaine).

OBJECTIVE

The purpose of this investigation is to develop a predictive mathematical model that can identify cardiac sensitizers.

APPROACH

The dog and the swine were used as surrogates for the human. Physiologic and electrocardiographic measurements were taken during the control period and after each dose of ouabain, a digitalis glycoside known to provoke ventricular arrhythmia. Logistic regression was used to develop the model by converting binary data into a function (curve/equation) that can estimate of the probability of a particular result, in this case experiencing a cardiac arrhythmia.

RESULTS

Five parameters were significant predictors of arrhythmia in dog. These included heart rate (HR), PQ interval (PQ), QT interval (QT), systolic aortic pressure (Paos) and estimation of contractility (dP/dt_{ma}). Three parameters were significant in the swine (PQ, QT and dP/dt_{ma}). The study demonstrates that several mathematical models can be constructed to predict the onset of ouabain induced arrhythmia, in both the dog and the swine, and that there are similarities in the two animal models. Efforts to reduce the number of parameters to a single term showed colinearity among simple pair wise combinations.

CONCLUSION

Since the QT interval was significant in both species it appears to be the most promising of all the parameters for predicting cardiac sensitization.

ABSTRACT

Cardiac sensitization is the sensitization of the heart to circulating catecholamines after exposure to an exogenous chemical, such that sudden alarm or exercise may precipitate a cardiac arrest. The purpose of this investigation is to develop a predictive mathematical model that can identify cardiac sensitizers. The dog and the swine were used as surrogates for the human. Physiologic and electrocardiographic measurements were taken during the control period and after each dose of ouabain, a digitalis glycoside known to provoke ventricular arrhythmia. Logistic regression was used to develop the model by converting binary data into a function (curve/equation) that can estimate of the probability of a particular result, in this case experiencing a cardiac arrhythmia. Five parameters were significant predictors of arrhythmia in dog (HR, PQ, QT, Paos and dP/dt_{max}), and three were significant in the swine (PQ, QT and dP/dt_{max}). The study demonstrates that several mathematical models can be constructed to predict the onset of ouabain induced arrhythmia, in both the dog and the swine, and that there are similarities in the two animal models. Efforts to reduce the number of parameters to a single term showed colinearity among simple pair wise combinations. Since the QT interval was significant in both species, it appears to be the most promising of all the parameters for predicting cardiac sensitization.

KEY WORDS

Cardiac Sensitization, Ventricular Arrhythmia, Dogs, Swine, Ouabain

LIST OF ABBREVIATIONS

Note common chemical and measurement abbreviations are not included.

HR	heart rate (beats/minute)
PQ	PQ interval (sec)
QT	QT interval (sec)
$dP/dt_{max.}$	estimation of contractility (mm or mmHg/s)
$dP/dt_{min.}$	estimation of lusitropy (mm or mmHg/s)
Paos	systolic aortic pressure (mmHg)
Paod	diastolic aortic pressure (mmHg)
Paom	mean aortic pressure (mmHg)
LVED	left ventricular end-diastolic pressure
Peak	peak aortic blood flow (cm/sec)
DT	duration time of left ventricular ejection (sec)
TVI	time velocity integral (cm)
CO	TVI*HR
Z	dPao/dF
SVR	Poam/CO

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INTRODUCTION

Cardiac sensitization is a specialized physiological condition. In its simplest terms, it is the sensitization of the heart to circulating catecholamines (i.e. epinephrine) after exposure to an exogenous chemical, such that sudden alarm or exercise may precipitate a cardiac arrest (Adgey et al., 1995). The main mechanism of cardiac arrest is a cardiac arrhythmia, although anoxia, respiratory depression, and vagal stimulation along with aspiration of vomit or trauma may be contributing factors leading to sudden death. The most prevalent example of cardiac sensitization is the recreational abuse of solvents, commonly known as "Huffing" or "Sniffing" (Bass, 1970). Chemicals that have a known cardiac sensitizing potential include: fuel gases (butane, propane, and gasoline vapors); other solvents such as typewriter correction and dry cleaning fluids (trichloroethane); fire extinguishers (bromochlorodifluoromethane); degreasing agents (trifluorotrichloroethane); adhesives (toluene); aerosol propellants (halons and/or butane); and medications (digitalis glycosides and cocaine) (Adgey et al., 1995, Kaufman et al., 1994, Mest et al., 1995, Ohuoha et al., 1998).

The test currently accepted by federal regulators to determine a chemicals' cardiac sensitization potential exposes beagle dogs to the chemical of interest and then challenges the animal with a predetermined titrated dose of epinephrine (U.S. EPA 1994). During the titration, chemical exposure, and epinephrine challenge periods, an electrocardiogram (ECG) on the animal is monitored for ectopic beats. An ectopic beat is a premature contraction of the heart prior to the time that a normal contraction would have been expected. Numerous ectopic beats can disrupt the cyclic nature of the heart. The concentration at which ectopic beats are first observed establishes the level at which cardiac arrhythmias may be expected under stressful conditions.

When the cardiac sensitization model was developed, the physical observation of ectopic beats was clearly the most obvious endpoint (parameter) by which to measure a chemical's sensitizing effect on the heart. Although several in vitro models have been attempted to predict cardiac sensitizers, a better understanding of the mechanism behind cardiac sensitization is needed. The primary objective of this investigation is to construct a mathematical model that is capable of predicting clinical conditions of cardiac arrhythmia before the onset of cardiac arrest.

As a first step, 15 cardiac physiological parameters were evaluated prior to the development of cardiac arrest (arrhythmia). A corollary to this objective is to determine if anesthesia in any way obfuscates the ability of physiological monitoring to predict the onset of arrhythmia.

METHODS AND MATERIALS

ANIMALS

Six male (10 kg) beagle dogs and six male (25 kg) Yorkshire swine were used.

PHYSIOLOGICAL PARAMETERS

A combination of hemodynamic and electrophysiologic parameters was measured during a baseline state (control) and immediately prior to arrhythmia. The parameters are as follows:

1) HR, beats/minute
2) PQ interval, sec
3) QT interval, sec
4) dP/dt_{max}, mm or mmHg/s
5) dP/dt_{min}, mm or mmHg/s
6) Paos (systolic aortic pressure), mmHg
7) Paod (diastolic aortic pressure), mmHg
8) Paom (mean aortic pressure), mmHg
9) LVED (left ventricular end-diastolic pressure)
10) Peak (peak aortic blood flow), cm/sec
11) DT (duration time of left ventricular ejection), sec
12) TVI (time velocity integral), cm
13) CO, TVI*HR
14) Z, dPao/dF
15) SVR (Poam/CO)

Pulsatile aortic (AP) and left ventricular pressures (LVP), dLVP/dt, pulsatile aortic flow, and its integral (SV) were recorded on a direct-writing photographic oscillograph and FM tape. Aortic impedance was estimated by dividing pulsatile aortic pressure by pulsatile flow (i.e. stroke volume), and systemic vascular resistance was estimated by dividing mean systemic arterial pressure (presuming right atrial pressure was constant) by cardiac output. To estimate contractility and lusitropy, respectively, dP/dt_{max} and dP/dt_{min} were used, realizing that both methods are load dependent. ECGs were analyzed for heart rate (chronotrope), and PQ (dromotrope), and QT (repolarization) duration.

CHEMICAL/DRUG

Ouabain, a digitalis glycoside, was used to provoke ventricular arrhythmia. Pigs were anesthetized with thiopental-halothane; and dogs with thiopental-chloralose.

DOG STUDY

The experimental design was adopted from Robitaille, *et al.*, 1993; Rath, *et al.*, 1995; and Josephson, 1992. Prior to the start of the study, each dog was anesthetized with thiopental-halothane. Catheter-introducers were placed in a jugular vein and a carotid artery. Animals were allowed to recover after the surgery. Prior to exposure to ouabain, a pacing catheter was introduced through the jugular vein with the bipolar leads being positioned in the right ventricle. A Millar catheter containing two solid-state pressure transducers and a flowmeter was introduced through the carotid artery. One of the pressure transducers was positioned in the left ventricle and the other in the ascending aorta with the flowmeter. Electrodes forming lead II ECG were placed on the limbs of the animals. During the first phase of the dog study, the parameters were measured in conscious dogs. Each animal was dosed, intravenously, with 40 mg/kg ouabain (priming dose). Additional doses of 0.15 mg/kg ouabain were given every 15 minutes (graded doses) until ventricular arrhythmia was produced. All parameters were measured during the baseline period (control), after infusion of the priming dose and after each graded dose. Before each ouabain infusion, the right ventricle was paced ten times (eight conditioning stimuli at 300 ms intervals, the 9^{th} stimulus at 150 ms interval, and the 10^{th} stimulus at 130 ms interval) to determine if non-paced ventricular ectopic activity (termed RVR for repetitive ventricular responses) occurred. The end-point of each experiment was taken when the dog developed the first ventricular premature depolarization, either spontaneously or after cessation of pacing. For the second phase of the dog study, the same animals were anesthetized 24-hours later. The dogs were anesthetized intravenously with thiopental sodium (15 mg/kg) and alpha chloralose (100 mg/kg), and measurements were made as in the first phase. Upon completion, the dogs were euthanized before awakening.

SWINE STUDY

The swine were evaluated only under anesthesia. The model used was the same experimental procedure used for the second phase of the dog study.

STATISTICAL METHODS

These data were evaluated using logistic regression since the outcome variable is binary (Neter *et al.*, 1983). The outcome variable was defined as baseline or prior to arrhythmia. The analysis was performed using the logistic procedure in SAS (Cary N.C, 1999). The independent variables in the model for evaluating the effect of anesthesia on dogs were the parameters measured and "Group." The dependent variable was assigned a value of "zero" for control or a value of "one" for the onset of arrhythmia. A significance level of 0.10 was chosen as an inclusion criterion, since this study was to investigate the feasibility of building a predictive model. Logistic regression is given by equation 1 with p being the probability of arrhythmia, X_1 the corresponding cardiac parameter measurement, and β_0, β_1 and β_2 the parameters of the logistic function to be estimated. Group (X_2) is given a value of "one" for conscious or "two" for anesthetized.

$$p = \frac{e^{\beta_0+\beta_1 X+\beta_2 Group}}{1+e^{\beta_0+\beta_1 X+\beta_2 Group}} \qquad \text{(Equation 1)}$$

The output from SAS includes the β_0, β_1 and β_2 estimates, p-value for these estimates, and a p-value for assessing goodness-of-fit for the model using -2 Log Likelihood as the criteria, which has a chi-square distribution under the null hypothesis.

For the swine study the logistic regression equation is simplified and given by equation 2

$$p = \frac{e^{\beta_0+\beta_1 X}}{1+e^{\beta_0+\beta_1 X}} \qquad \text{(Equation 2)}$$

where p is the probability of arrhythmia, X_1 the corresponding cardiac parameter measurement, and β_0 and β_1 are the parameters of the logistic function to be estimated.

RESULTS

DOG STUDY

The first step in evaluating the model was to examine the p-value for the goodness-of-fit. Those parameters whose goodness-of-fit were significant included HR, PQ, QT, Paos, and dP/dt_{max}. Table 1 contains these results. Further examination showed that the models for HR, PQ, QT, and Paos were significant with respect to the parameter. These same models were not significant with respect to the "Group" factor, indicating that there was no difference between data from conscious or anesthetized dogs. Because it fulfilled the criteria for significance with respect to goodness-of-fit as well as the predicting arrhythmia, dP/dt_{max} was still included as a model. Figures 1 and 2 illustrate significant and non-significant models. Twenty-two observations were made during this study; these included two readings (baseline and prior to arrhythmia) for five conscious animals and two readings (baseline and prior to arrhythmia) for six anesthetized animals. Due to technical difficulties, the values for one animal during the conscious phase of the study are missing.

SWINE STUDY

Starting with goodness-of-fit, QT and PQ were significant. Table 2 contains these results. Further examination showed that the model for QT was significant with respect to the parameter. Since PQ passed the goodness-of-fit test, it was included as a model, even though its p-value with respect to parameter was not significant at the 0.1 level. Because there was complete separation in baseline data and data prior to arrhythmia, dP/dt_{max} produces no unique logistic function (figure 3) However, this does not mean that it is not a significant predictor for cardiac arrhythmia.

DISCUSSION

The objective of this investigation is to construct either a single or series of mathematical model(s) that can predict a chemical's potential as a cardiac sensitizer. The model is based upon physiological measurements prior to the onset of cardiac arrhythmia. The measurements were

separated into baseline and arrhythmicgenic responses. Ouabain, a digitalis glycoside, was selected for this study because of its ease of use and documentation as a cardiac sensitizer (Mest *et al.*, 1995; Lotan *et al.*, 1992; Mest *et.al.*, 1992; Mest and Balewska, 1991; Thomas and Varma, 1991). It is a potent parasympathomimetic with positive inotrope and negative doromtrope behavior. Programmed electrical stimulation (PES) was selected in place of epinephrine because repeated use of an arrhythmic dose of epinephrine may result in myocardial damage (Van-Belle *et al.*, 1992; Herbaczynska-Cedro and Gajkowska, 1992; Prichard *et al.*, 1991).

In constructing the model, our focus was to develop a bridge between the current dog model and a predictive mathematical model. In order to develop the most humane procedure, it had to be determined if anesthesia would exert any effect on the physiological parameters chosen to be measured. The current model uses conscious dogs. Comparing data from conscious and anesthetized dogs suggest that anesthesia has no significant effect on the physiological parameters measured. This was evident by the lack of significance for the factor "Group," which designated data as conscious or anesthetized in the statistical argument. Determining if anesthesia would obfuscate the results became crucial for future studies that would involve swine, the second and confirming (supportive) animal model.

Conventional inferential statistics only determine if control values for each parameter are significantly different from their corresponding experimental values. The goal was for the model to provide an estimate of the probability for an arrhythmicgenic response, hence, the use of logistic regression. Logistic regression takes binary data (baseline/arrhythmia) and converts it to a function (curve/equation) that can estimate of the probability of a particular result, in this case, experiencing a cardiac arrhythmia. This approach allows the user to predict, at a given dose, the predisposition of an individual to an arrhythmicgenic response. The only limitation of logistic regression is in the event all control values and experimental values are contained in intervals, such that there is no overlap with each other. In this situation, there is no single logistic function, which will describe the data. Instead, there are an "infinite" number of functions which could describe the data.

For the dog, functions for each of the five parameters (HR, PQ, QT, Paos, and dP/dt_{max}) were found to be significant predictors for cardiac arrhythmia. Data for each parameter can be

measured via non-invasive procedures (electrocardiograms and pressure cuff). Although all five parameters were individually predictive of arrhythmia, their combinations provide no increase in predictive powers. As shown in Table 3, the goodness-of-fit test is significant for each pair wise comparison and the "Group" factor indicates that there was no difference between data from conscious or anesthetized dogs. However, simple pair wise combinations show that there is colinearity among the five parameters, illustrating a lack of independence.

Swine were selected as the second animal model to confirm the findings in the dog, as well as being a transition model for humans. Swine have a cardiovascular system similar to that of humans. For the swine, only QT was found to be a significant predictor for cardiac arrhythmia. PQ was marginally significant. PQ, and dP/dt_{max} were significant but did not produce a unique function. However, for the dog study, there were twice as many observations (conscious and anesthesized) as in the swine. By increasing the number of observations in the swine, more parameters may become significant. Therefore, there was no attempt to examine pair wise comparisons.

This study suggests that the QT interval, the PQ interval, and dP/dt_{max} are the most promising of all parameters for predicting cardiac sensitization. Since the QT interval was the only parameter significant in both the dog and the swine, it is the leading model for predicting cardiac sensitization among multiple species. Additional research is needed in this area, however this paper sets the foundation for a comprehensive predictive mathematical model, regardless of species.

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TABLE 1. Results of Multiple Logistic Regression (coefficients and p-values) for Predicting Cardiac Arrhythmia in Conscious and Anesthetized Dogs

Model	Intercept (β_0) (p-value)	Parameter (β_1) (p-value)	Group (β_2) (p-value)	GOF* (p-value)	Number of Obs
HR	10.9995 **(0.05)**	-0.1074 **(0.03)**	-0.7800 (0.58)	15.5560 **(<0.01)**	22
PQ	-11.6561 **(0.05)**	131.600 **(0.04)**	-1.8058 (0.21)	11.2960 **(<0.01)**	22
QT	-9.2750 **(0.04)**	41.0680 **(0.02)**	-2.0673 (0.20)	15.1040 **(<0.01)**	22
DP/dT_{max}	-21.2588 **(0.03)**	0.5570 **(0.02)**	4.9337 **(0.07)**	14.5820 **(<0.01)**	22
DP/dT_{min}	-5.8093 (0.13)	0.2858 (0.09)	0.0798 (0.94)	3.5660 (0.17)	22
Paos	-9.8166 **(0.06)**	0.0765 **(0.05)**	-0.9769 (0.41)	8.9350 **(0.01)**	22
Paod	-1.7436 (0.45)	0.0257 (0.34)	-0.3848 (0.69)	0.9630 (0.62)	22
Paom	-4.0873 (0.16)	0.0465 (0.10)	-0.6673 (0.50)	3.4160 (0.18)	22
LVED	-1.3440 (0.43)	0.1998 (0.15)	-0.3497 (0.71)	2.4640 (0.29)	22
Peak	-2.3822 (0.33)	0.0197 (0.22)	0.2790 (0.76)	1.6250 (0.44)	22
DT	-0.7526 (0.76)	6.4402 (0.72)	-0.1368 (0.88)	0.1320 (0.94)	22
TVI	-1.3587 (0.47)	0.1836 (0.27)	-0.0091 (0.99)	1.2710 (0.53)	22
CO	2.5104 (0.23)	-0.0033 (0.08)	-0.2572 (0.79)	3.5900 (0.17)	22
Z	-1.5933 (0.38)	3.0612 (0.14)	-0.2079 (0.82)	3.1950 (0.20)	22
SVR	-0.9861 (0.54)	8.9137 (0.06)	-0.5768 (0.56)	4.8060 (0.09)	22

* = goodness-of-fit (GOF) for the model using -2 Log Likelihood as the criteria, which has a chi-square distribution under the null hypothesis

TABLE 2. Results of Multiple Logistic Regression (coefficients and p-values) for predicting Cardiac Arrhythmia in Swine

Model	Intercept (β_0) (p-value)	Parameter (β_1) (p-value)	GOF* (p-value)	Number of Obs
HR	2.0074 (0.54)	-0.0188 (0.53)	0.4160 (0.52)	12
PQ	-17.5096 (0.13)	152.7000 (0.13)	5.5710 **(0.02)**	12
QT	10.1593 **(0.11)**	-32.6935 **(0.10)**	15.5560 **(<0.01)**	12
DP/dTmax	***	***	***	12
DP/dTmin	NA	NA	NA	
Paos	-4.5428 (0.44)	0.0483 (0.44)	0.6660 (0.42)	12
Paod	2.3835 (0.63)	-0.0383 (0.63)	0.2440 (0.62)	12
Paom	-0.0831 (0.99)	0.0011 (0.99)	0.0001 (0.99)	12
LVED	0.0713 (0.96)	-0.0060 (0.96)	0.0030 (0.96)	12
Peak	**NA**	NA	NA	
DT	5.4580 (0.33)	-23.7102 (0.32)	1.1230 (0.29)	12
TVI	NA	NA	NA	
CO	-1.5297 (0.64)	0.4302 (0.64)	0.2320 (0.63)	12
Z	-4.8077 (0.37)	5.1124 (0.38)	1.4530 (0.63)	12
SVR	-0.1028 (0.95)	0.0045 (0.95)	0.004 (0.95)	12

* = goodness-of-fit (GOF) for the model using -2 Log Likelihood as the criteria, which has a chi-square distribution under the null hypothesis

*** = Because there was complete separation in baseline data and data prior to arrhythmia, dP/dt_{max} produces no unique logistic function

NA = not available

All values are mean ± standard deviation

* significantly different from all other methods at $p \leq 0.05$.

TABLE 3. Pairwise comparison of the five significant parameters in the dog. Results are given as p-values

Parameters	Likelihood	Intercept	Group	Parameter 1‡	Parameter 2
HR & PQ	<0.0001	*	*	*	*
HR & QT	0.0002	0.7610	0.2131	0.1208	0.1152
HR & Paos	0.0003	0.9539	0.4707	0.0570	0.2984
HR & dP/dt_{max}	<0.0001	*	*	*	*
PQ & QT	0.0003	0.0401	0.1365	0.1758	0.0683
PQ & Paos	0.0001	0.0817	0.1140	0.1661	0.0479
PQ & dP/dt_{max}	0.0006	0.0292	0.4127	0.2256	0.0576
QT & Paos	<0.0001	0.1115	0.2916	0.0522	0.2237
QT & dP/dt_{max}	<0.0001	*	*	*	*
Paos & dPdT	0.0013	0.0271	0.2295	0.3579	0.0670

‡ **Parameter 1 is the first parameter in the pair (i.e. HR & PQ: Parameter 1 is HR and Parameter 2 is PQ)**

* means that there was complete separation in 2-space, i.e. not unique solution

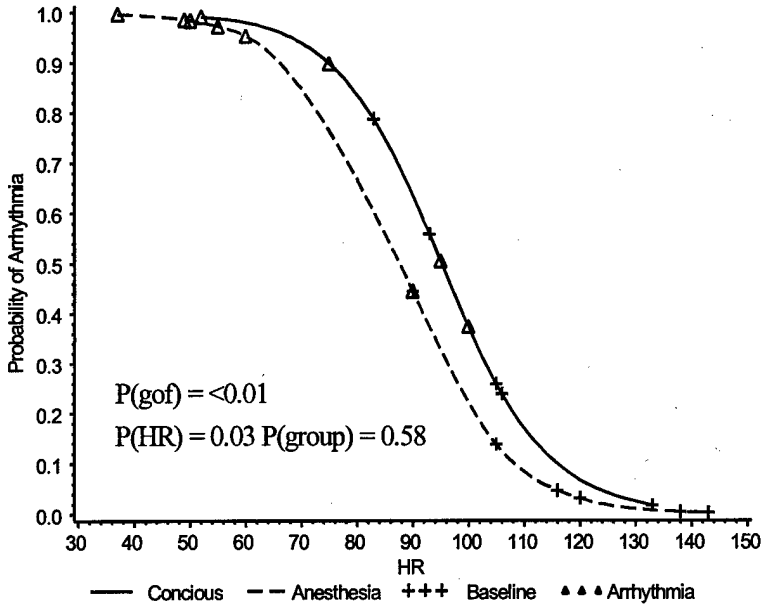

Figure 1. Heart Rate : Dog (Conscious vs. Anesthetized).

Comparison of probabilities for the onset of arrhythmia based on the heart rate (HR) of conscious and anesthetized dogs. (GOF = goodness-of-fit).

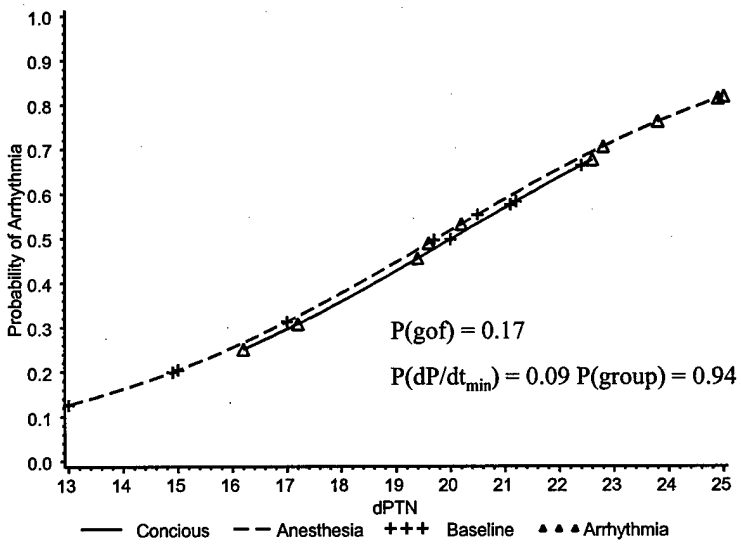

Figure 2. dP/dt_{min} : Dog (Conscious vs. Anesthetized).

Comparison of probabilities for the onset of arrhythmia based on the dP/dt_{min} of conscious and anesthetized dogs.

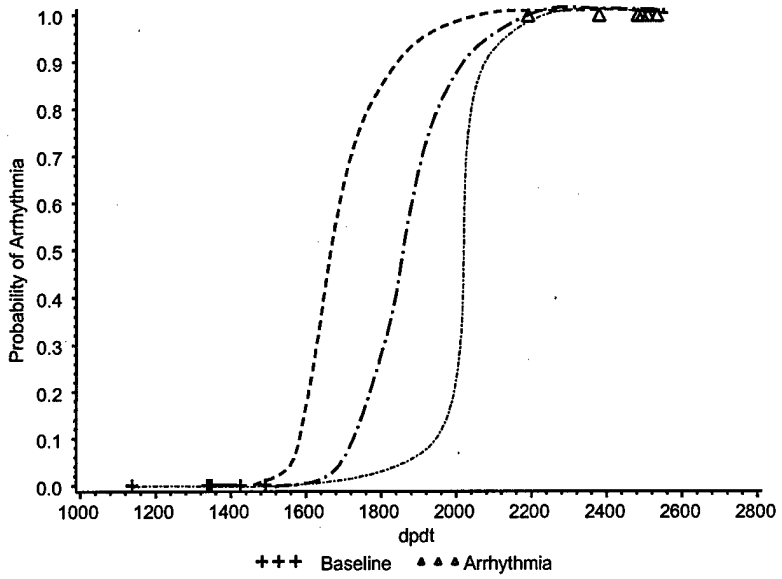

Figure 3. dP/dt_{max} : Pig.

Possible graphical representations for dP/dt_{max} in swine. Because there was complete separation in baseline data and data prior to arrhythmia, dP/dt_{max} produces no unique logistic function. This however, this dose not mean that it is not a significant predictor for cardiac arrhythmia. Hence, all lines drawn in figure 3 are possible functions for dP/dt_{max}.

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6. **AUTHOR(S)** E. Smith, T. Nakayama, E. Herderick, J. Powers, G. Briggs, K. Still, and R. Hamlin			
7. **PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)** Naval Health Research Center Detachment Toxicology NHRC/TD 2612 Fifth Street, Building 433 Area B Wright-Patterson AFB, OH 45433-7903			8. **PERFORMING ORGANIZATION REPORT NUMBER**
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13. **ABSTRACT** *(Maximum 200 words)* Cardiac sensitization is the sensitization of the heart to circulating catecholamines after exposure to an exogenous chemical, such that sudden alarm or exercise may precipitate a cardiac arrest. The purpose of this investigation is to develop a predictive mathematical model that can identify cardiac sensitizers. The dog and the swine were used as surrogates for the human. Physiologic and electrocardiographic measurements were taken during the control period and after each dose of ouabain, a digitalis glycoside known to provoke ventricular arrhythmia. Logistic regression was used to develop the model by converting binary data into a function (curve/equation) that can estimate of the probability of a particular result, in this case experiencing a cardiac arrhythmia. Five parameters were significant predictors of arrhythmia in dog (HR, PQ, QT, Paos and dP/dt_{max}), and three were significant in the swine (PQ, QT and dP/dt_{max}). The study demonstrates that several mathematical models can be constructed to predict the onset of ouabain induced arrhythmia, in both the dog and the swine, and that there are similarities in the two animal models. Efforts to reduce the number of parameters to a single term showed colinearity among simple pair wise combinations. Since the QT interval was significant in both species, it appears to be the most promising of all the parameters for predicting cardiac sensitization.

14. **SUBJECT TERMS** Cardiac Sensitization, Ventricular Arrhythmia, Dogs, Swine, Ouabain			15. **NUMBER OF PAGES** 30 16. **PRICE CODE**
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